REMARKS

Claims 4, 5, 10-13 and 15-23 are pending the application; Claims 11-13 and 15-23 are withdrawn; Claims 4, 5 and 10 stand rejected. By this Amendment, Claims 11-13 and 15-23 have been cancelled, Claims 4 and 5 have been amended and new Claims 28-32 have been added. These amendments and new claims add no new matter to the application.

Claims 4-5 and 10 stand rejected under 35 USC §102 as allegedly anticipated by Castillo WO 98/51302, by JP 10245342 (Mitsui Norin), or by JP 10-175858 (Takami); Applicant respectfully traverses these rejections. Amended claims 4 and 5 now require selection of a therapeutic substance that can only be either green tea, green tea leaves or green tea extract, and none of the new claims require the use of epicatechin. Castillo does not make any mention of these now claimed substances at all, much less as efficacious in anti-fibrillogenesis. Castillo thus does not anticipate claims 4-5 and 10, or any of the new claims. In addition, Claim 10 depends from claim 4 and properly construed contains all the limitation of claim 4, and is therefore not anticipated either; moreover, claim 10 further requires the presence of at least one of the substances, ginkgo biloba, rosemary, gotu kola, bacopin or ginseng, and Castillo makes no mention whatever of these substances. These claims are therefore all believed to be allowable over Castillo, and reconsideration is requested.

Independent claim 4 and all new claims all now require either green tea, green tea leaves or green tea extract. Mitsui Norin makes no mention of fibril formation at all (see argument below). Mitsui Norin only teaches narrowly that a certain kind of nerve cell toxicity that is supposedly caused by beta-amyloid protein, can possibly be reduced with tea polyphenols. (See also the Rule 132 Declaration of Dr. Alan Snow filed July 28, 2003.)

Takami also makes no mention of fibril formation at all (see argument below). Takami only teaches narrowly that a certain kind of active oxygen toxicity can be reduced by disclosed

extracts of green tea containing various catechins. Nothing beyond a passing reference is said about Alzheimer's disease, and certainly nothing about treating amyloid fibrils.

The Examiner is implying that Aß nerve cell toxicity, or reduction of active oxygen, NECESSARILY (that is, 'inherently') teaches an effect on the treatment of Aß fibril formation, deposition, accumulation and/or persistence. But Dr. Snow states in his declaration that the literature does not support such an implication of necessary effect on Aß fibril, as is set forth in more detail below.

Dr. Snow says in his declaration that at least one study by Wang (Wang, The Neuroprotective Effects of Phytoestrogens on Amyloid ß Protein-induced Toxicity Are Mediated by Abrogating the Activation of Caspase Cascade in Rat Cortical Neurons, J. Biological Chem., vol 276 no 7, pp 5287-5295, February 16, 2001) (copy was attached to Snow Declaration) reports that "although Aß mediated neurotoxicity [is a] focus of intense interest, the underlying mechanisms are still controversial" (see p 5294, col 2 below fig. 9). Wang thus reports that no necessary inferences may be drawn from any study of Aß mediated neurotoxicity, and the Examiner has cited no authority to the contrary.

Wang also reports that nerve cell death or neurotoxicity is in fact the result of a cascade involving caspases and reactive oxygen species accumulation (see abstract p 5287 - near end). Also, Zhang (Zhang, Selective Cytotoxicity of Intracellular Amyloid ß Peptide 1-42 Through p53 and Bax in Cultured Primary Human Neurons, J. Cell Bio., vol 156 no 3, pp 519-529, February 3, 2002) (copy was attached to Snow Declaration) reports that nonfibrilized and fibrilized Aß are equally toxic (see p 519, midway thru abstract), and corroborates Wang in suggesting a caspase cell death route (see p 525, col 1, 1st paragraph). This is further refutation of anything that might be regarded as a "necessary" suggestion that inhibition of Aß neurotoxicity may be useful in treating Aß fibril formation, deposition, accumulation and/or persistence. There

is likewise no suggestion in any of the literature that fibrillogenesis plays any part whatever in the reported cell death.

Wang even reports that the high antioxidant activity of flavanoids *per se* was not able to protect neurons against Aß-induced neurotoxicity (see p 5292, col 1, end of penultimate paragraph); thus teaching away from a suggestion that flavanoids might be useful in preventing Aß fibrillogenesis.

There are thus no necessary inferences to be drawn from the cited studies pertaining to neuronal cell death or active oxygen reduction as to Aß fibrillogenesis, because in at least some of the reported studies, the causes of the cell death do not involve any effect on Aß fibrillogenesis. There is thus no implication available to serve as a teaching that inhibition of nerve cell death or nerve cell toxicity by Aß inherently leads to treating Aß fibril formation, deposition, accumulation and/or persistence.

Therefore none of the claims inherently read on any of teaching of the cited references. Applicant respectfully submits that the cited doctrine of inherency therefore does not apply to the rejected method claims.

The Examiner is also respectfully directed again to review the following Federal Circuit authority on the subject of inherency. This reviewing court which sets the law to which both Applicant and the PTO must adhere, has already determined that some kinds of apparent "inherency" do not justify a rejection of claims. *In re Randall Wright*, 848 F.2d 1216, 6 USPQ2d 1959 (Fed.Cir. 1988). The Court says all cases must be decided on their own facts, and goes on to say, while reversing a PTO inherency rejection of claims not unlike the one presented in this application,

> Thus the question is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working. *Rinehart*, 531 F.2d at 1054, 189 USPQ at 149; see also *In re Benno*, 768 F.2d 1340, 1346, 226 USPQ 683, 687 (Fed.Cir. 1985) ("appellant's

> problem" and the prior art "present different problems requiring different solutions").
>
> The problem upon which Wright was working was improving the pitch-measuring capability of the level, not the visibility of the bubble. The PTO, having conceded that Wright's structure was unobvious for his intended purpose, erred in holding that this was not relevant. The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered. [Emphasis added]

Wright, 848 F.2d at 1219. Just as in the *Rinehart* and *Wright* cases above, so also in this case, "[Applicant's] problem and the prior art present different problems requiring different solutions". It has to be relevant that the problem solved by Applicant (treatment of amyloid fibrils) is not the problem addressed by the cited references (nerve cell toxicity and cell death). Under the law of the Federal Circuit, which is the law the binds the PTO, the rejected claims are therefore not "inherently" present in the cited references, and they therefore must be allowed over the cited art.

The specific limitations of the rejected claims must therefore all be read in any attempt to read any of the claims upon any prior art methods, and the claimed methods, especially as now amended, all differ markedly from the teachings of the cited references. The Examiner asserts that the cited references teach the same method steps that are claimed in this case, but that is not so. The rejected claims are directed to

It is also the case that, in the claimed method steps, the step of administering a therapeutic amount (or a therapeutically effective amount) of a selected substance alone is a step that is different from any implied step in any of the cited references, since whatever amount might be therapeutic in treating cell death or neurotoxicity (as taught by Mitsui Norin), or active oxygen (as taught by Takami), is not necessarily therapeutic for any of the amyloid fibrillogenesis involved in the therapeutic targets of the rejected claims. (See again Snow Declaration, and the *Wright* case.)

In passing, Applicant also traverses what the Examiner characterizes as an admission of prior art on page 5, lines 13-16 of the specification; Applicant discloses that catechins are present

in green tea, as part of Applicant's report of it's own discoveries, and does not therein admit that such knowledge was already prior art at the time of disclosure. It is also submitted that the Examiner is reading into the Mitsui Norin reference something more than it actually contains, when he states that it teaches giving green tea extract "to a subject suffering from Alzheimer's disease so as to inhibit senile plaque formation due to deposition of beta-amyloid protein on brain nerve cells" so that the toxicity of beta-amyloid protein is reduced; in fact, Mitsui Norin makes no reference whatever to any of these processes. It is clear that Applicant is the only one disclosing treatment and reduction of amyloid fibrils through the use of green tea extract.

Claims 4, 5 and 10 are also rejected under 35 USC 103 over Mitsui, Takami or Castillo, in view of Chatterjee, and the recognized state of the art; Applicant respectfully traverses these rejections as well. It appears the 103 argument is only directed to claim 10, and is dealt with accordingly here. Primarily for reasons already argued above, none of the cited references, nor any combination of them, make obvious the combination of steps and substances in claim 10, as no combination of references teaches or suggests all of the steps and substances of claim 10. Claim 10 properly read contains all the limitations of Claim 4, and as such, all cited references fail to suggest the combination of steps and substances actually claimed. The rejected claims are therefore all believed to be non-obvious and allowable over the cited art, and reconsideration is requested. Applicant also traverses the Examiner's unsupported supposition that any of the listed ingredients are known in the art to be efficacious in treating amyloid fibrils; Applicant asserts that it alone has discovered and claimed this efficacy.

Amended Claim 4 recites two distinct method steps not disclosed in any cited reference,:

> "the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes ... " and

"such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils."

The presence of these distinct method steps alone make the cited doctrine of inherency inapplicable, because even if it could be applied in this case, it could not be applied to a claimed method where the method steps themselves are not covered in the references. In addition, Claim 4 now no longer recites epicatechin, and it no longer recites inhibition or management of fibrils, which, as suggested by the Examiner, narrows the applicability of the cited references because we are not claiming the case where fibrils are not already present in the subject. For these additional reasons, Claim 4 and its dependents are all believed to be allowable and reconsideration is requested.

New Claim 28 is akin to Claim 4, but includes an express recitation that the fibrils to be treated are already existing. Claim 28 and its dependents are therefore also believed to be allowable.

New Claim 31 is akin to amended Claim 4, but includes the express recitation of several new process steps by which the therapeutic substances are to be derived. It is believed that these explicit process steps among others, which are novel over any process disclosed by the cited art, render the claim allowable. Claim 31 now requires that the substances to be administered be created by (1) a water extraction using water that is not boiling of one the substances selected from green tea, green tea leaves, and green tea extract, and (2) separation and lyophilization of the supernatant from the extract. These processes, which are set forth in Example 1 of the specification, are distinct from the extraction processes taught by the references. For instance, in Mitsui in paragraph 0027, the green tea extraction is only taught to proceed either by boiling water extraction or by boiling alcohol or acetone extraction. These are significantly different extraction steps and likely to produce significantly different extracts. Mitsui then teaches separation of the extract by HPLC or by organic solvent dilution. This is a different step entirely

from the claimed simple separation of supernatant and lyophilization. Accordingly, Claim 31 is neither anticipated or rendered obvious by any of the cited references, and early allowance is requested.

Applicant also traverses the double patenting rejection, submitting that with the amendments it is now moot, as there is no epicatechin that is claimed.

The rejected claims and new claims are therefore all believed to be allowable over the art of record, and reconsideration is requested.

Applicant believes that it has responded fully to all of the concerns expressed by the Examiner in the Office Action, and respectfully requests entry and examination of new claims and reexamination of all rejected claims and early favorable action on all pending as well. If the Examiner has any further concerns, Applicant requests a call to Patrick Dwyer at (206) 343-7074.

Respectfully submitted,

PATRICK MICHAEL DWYER
Reg. No. 32,411

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PATRICK M. DWYER
PROTEOTECH, INC.
1818 WESTLAKE AVENUE N, SUITE 114
SEATTLE, WA 98109